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EXAMINER	
SCHNIZER, RICHARD A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,726	KLIPPEL-GIESE ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-72* is/are pending in the application.

4a) Of the above claim(s) *57,58,61-64,66,67 and 69-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-56,59,60,65 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 April 2005 and 03 July 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was filed on 7/23/08.

All previously pending claims were canceled, and new claims 54-72 were added. The numbering of the instant claims is consistent with the requirement to renumber the claims (Action of 7/12/07).

Claims 54-72 are pending.

Newly submitted claims 57, 58, 61-64, 66, 67, and 69-72 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: they are drawn to non-elected antisense, aptamer, ribozyme, or spiegelmer embodiments

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 57, 58, 61-64, 66, 67, and 69-72 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 54-56, 59, 60, 65, and 68 are under consideration.

Rejections/objections not reiterated herein are withdrawn.

This Action is NON-FINAL due to new grounds of rejection not necessitated by amendment.

Claim Objections

Claim 56 is objected to “harmartoma” is misspelled in the third and fourth lines. The correct spelling is "hamartoma". See e.g. instant specification at page 17, line 5.

Claims 55 and 56 are objected to. Each of these claims is drawn to a method of inhibiting the growth of a tumor or a precancerous growth, and each recites a Markush group intended to list types of tumors or precancerous growths. However, each Markush group lists types of diseases or syndromes which may be characterized by tumors or precancerous growths, but are not per se tumors or precancerous growths. For example, Cowden’s syndrome, Li-Fraumeni syndrome, Bannayan-Zonana syndrome, and Lhermite-Duklos syndrome are diseases characterized by tumors or precancerous growths, but they are not tumors or precancerous growths per se. The objection could be overcome by amending the preambles to recite “the method of claim 54 wherein the subject suffers from” and then listing the various conditions as alternatives.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 56 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 56 is indefinite because neither macrocephaly nor mental retardation is a tumor or a precancerous growth, as required by the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 54-56, 59, 60, 65, and 68 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 54-56, 59, and 60 are directed to methods of inhibiting the growth of a tumor or precancerous growth associated with dysregulation of PI-3-kinase signaling by administering to a subject a composition comprising an siRNA that inhibits the activity of PRF1. PRF1 was also known in the prior art as REDD1, RPT801, and HOG18.

Claims 65 and 68 are drawn to methods of controlling the metastatic or migrational activity of tumor or cancer cells by contacting such cells with a composition comprising an siRNA that inhibits the activity of PRF1.

None of the claims limits the mode of administration.

The instant invention is based on the observations that transcription of PRF1 is regulated by one or more of the diverse PI3K signaling pathways, and that inhibition of

PRF1 expression in PC-3 prostate cancer cells resulted in a decrease in cell growth. The specification presents evidence that this transcriptional activation occurs downstream of HIF1 alpha and Akt in two of the myriad PI3K pathways, and that PRF1 is located downstream of mammalian target of rapamycin (mTOR) in the PI3K network, but provides no further guidance as to the biochemical function of PRF1.

PI3Ks constitute a family of enzymes that respond to stimuli from various receptors to produce 3' phosphoinositide lipids that act as second messengers by binding to diverse cellular target proteins to influence a variety of cellular activities including proliferation, differentiation, chemotaxis, survival/apoptosis, intracellular trafficking, and glucose homeostasis. See Katso et al (Annu. Rev. Dev. Biol. 17: 615-675, 2001). Katso states that the factors that determine which cellular function is mediated by a PI3K are complex and may be partly attributed to the diversity that exists at each level of the PI3K signaling cascade, such as the type of stimulus, duration of stimulus, the isoform of PI3K, the nature and intracellular location of the second messenger lipids, and the developmental state of the cell or organism. Further, the spatial and temporal aspects of PI3K signaling, functional redundancy, and crosstalk with other signaling networks are also thought to influence the integration of a given stimulus. See abstract, and page 655, first paragraph of Perspective.

Fig. 1 at page 624 of Katso gives some idea of the enormous complexity of PI3K signaling. Stimuli, both positive and negative, include Fak, shear stress, Cbl, Ruk, tyrosine kinase receptors, cytokines, integrins, cadherin, and G protein coupled receptors. Second messenger PIP_3 interacts with diverse entities including BTK/Tec

kinases, PDKI, PKD, and GEFs. These interactions give rise to overlapping as well as independent cascades of activity that result in a variety of outcomes including proliferation, differentiation, chemotaxis, survival/apoptosis, trafficking, and glucose homeostasis. Note that many factors known to be involved in PI3K signaling are not even represented in the Fig (such as Akt and HIF1-alpha). Thus, those of skill in the art at the time of the invention recognized that the effects of PI3K signaling in a given cell were influenced by a complex multitude of factors that constitute nodes in a network of signaling cascades extending from PI3K that controls the activity of a variety of proteins and the transcription of various sets of genes. Possible outcomes of PI3K stimulation include opposing effects such as cellular proliferation to apoptosis.

The specification as filed teaches that PRF1 seems to be regulated by both the HIF alpha and AKT branches of the PI3K network and occurs downstream of mammalian target of rapamycin (mTOR). The specification indicates that a decrease in the expression or activity of PRF1 is suitable to put a cellular system into a condition corresponding to hypoxic conditions, which may lead to apoptosis, so inhibition of PRF1 can stimulate apoptosis for therapeutic purposes in tumor treatment. See pages 12 and 18 (paragraphs 56 and 70 of the published application). However, Fig. 1 of Katso discloses at least two other pathways by which PI3K can inhibit apoptosis (i.e. through stimulation of IKK or inhibition of BAD), and the relationship of these pathways to PRF1 is not known.

It is clear that not all aspects of the PI3K network are functional in all cells, so it follows that tumors that are caused by defects in separate PI3K pathways that are not

functional in the same cell would not be treatable by an agent that affects only one of the pathways. Furthermore, the pathway steps that lead directly to regulation of PRF1 transcription or activity were not completely understood at the time of filing, and neither were the pathway steps directly downstream of PRF1 expression and activity, and its possible interactions with other signaling pathways. Accordingly the effects of manipulating PRF1 expression were unpredictable and had to be determined on a case by case basis for different tumors.

Absent information regarding which pathways are operating in a given cell at a given time, it would be completely unpredictable as to whether inhibition of PRF1 would stimulate apoptosis or not, because the effects of PRF1 inhibition on the other relevant apoptosis-affecting pathways are unknown. The specification provides no guidance in this regard, except to indicate that because PRF1 is at a downstream point in the network, it should be close to the point of action and unintended consequences should be limited. However, the relationship of PRF1 to other branches of the PI3K network involved in apoptosis control was unknown at the time of filing, so the effects of PRF1 inhibition on cell survival were not predictable. Note also that status of PI3K independent signaling pathways that affect apoptosis and cell survival would need to be taken into account in order to accurately predict the effects of such inhibiting PRF1 (see Katso at page 656, last paragraph).

At the time the invention was filed, the in vivo function of PRF1 was not well characterized. Shoshani et al (Mol. Cell. Biol. 22(7): 2283-2293, 2002, of record) identified RTP801 (PRF1) as a novel gene encoding a protein without any defined

structural domains that was upregulated sharply in glioma cells in response to hypoxia. They showed that PRF1 could either promote, or protect cells from, apoptosis and that these functions of PRF1 were dependent on the context of the cell in which it was expressed. PRF1 protected two secondary tumor cell lines from apoptosis under conditions of rapid cell division, while promoting apoptosis in both of those lines, as well as in primary non-cancerous lung parenchymal cells in vivo, under non-rapidly dividing conditions. However, Shoshani did not make a generalized conclusion that PRF1 caused apoptosis in rapidly dividing cells, but instead concluded that the involvement of PRF in pathogenic disease was complex and noted the importance of further study regarding its roles in dividing and non-dividing cells. See abstract and page 2292, last three paragraphs. Thus, prior to the time of the instant invention, it was recognized that PRF1 could either promote or inhibit cellular proliferation, depending on the context in which it was expressed. The actual biochemical function of PRF1 in PI3K signaling, i.e. enzyme, binding factor, etc., and its relationship to other PI3K pathways affecting apoptosis was not known at the time of the invention. Absent more information as to the actual biochemical function of PFR1, and the further study indicated as important by Shoshani, it is considered unpredictable as to what would be the effects of PRF1 expression inhibition in cells generally in view of the complexity of the PI3K signaling network.

The post filing art provides further evidence of unpredictability regarding the role of PRF1 in proliferative disease. DeYoung et al (Genes Dev. 22: 239-251, 2008) showed that PRF1 (identified as REDD1) can contribute to tumor suppression in

secondary tumor cells. "In vitro, loss of REDD1 signaling promotes proliferation and anchorage-independent growth under hypoxia through mTORC1 dysregulation. In vivo, REDD1 loss elicits tumorigenesis in a mouse model, and down-regulation of REDD1 is observed in a subset of human cancers." See abstract and section entitled "*Endogenous REDD1 functions to suppress tumorigenesis in vivo*" at page 246. Note that DeYoung states that a similar frequency of REDD1 downregulation was observed in a comparison of normal prostate tissue to invasive primary prostate carcinomas (citing Lapointe (Proc. Nat. Acad. Sci. 101(3): 811-816, 2004)). DeYoung concludes that "[t]aken together, these findings support the view that the endogenous REDD1 pathway... functions as a tumor suppressor mechanism in vivo" (page 246, right column, end of first full paragraph). See also Fig. 8 on page 248, which presents a model for the activity of REDD1 as a tumor suppressor. Clearly, if PRF1 (REDD1) acts as a tumor suppressor in some cells, then one of skill could not have predictably used inhibitors of its activity to inhibit the growth of tumors or precancerous cells without further knowledge of the function of PRF1 in those particular cells.

Other prior art references provide a correlation between PRF1 expression and cancer cells as follows.

Riggins et al (US 20030207840, effective filing date 7/26/01 (US 60/307600)) identified several genes that were induced in a variety of tumor cells in response to hypoxia. These genes included HOG18 (SEQ ID NO: 5) which encodes a polypeptide identical to PRF1. Riggins suggests that conditions related to angiogenesis, such as tumor growth, could be treated by disrupting expression of HOG18. See abstract,

paragraphs 9, 13, 22, 32, 33, 37, and 47; SEQ ID NOS: 5 and 6; and claims 12-14. Riggins does not provide a working example of tumor growth inhibition.

Monahan et al (US 20050037010, effective filing date 8/20/02 (US 60/404770)) taught that PRF1 (termed M22A or RTP801 by Monahan) was overexpressed in cervical cancer cells compared to normal cervical cells, and suggested that tumors could be treated with antisense that inhibits PRF1 expression. See paragraphs 62, 113, 159, 365, 368, and 371; SEQ ID NOS: 39 and 40; Table 1 at page 37; Table 5 at last line of page 38; Table 8 on page 40; and claim 40. Monahan does not provide a working example of tumor growth inhibition.

Faris et al (US 6673545) disclosed that a nucleic acid encoding instant PRF1 was overexpressed in metastatic prostate adenocarcinoma cells, relative to non-metastatic prostate adenocarcinoma cells. See Table 1 and column 4, lines 12-23. The nucleic acid is disclosed as SEQ ID NO: 45, also denoted in Table 4 as clone ID 3120209.

In view of the facts that, at the time of the invention, the control of the cell cycle by PI3K-mediated events was considered to be extremely complicated, the role of PRF1 in this process was incompletely understood, the biochemical function of PRF1 was unknown, and PRF1 was observed to elicit opposite effects on cell survival in different contexts, it is considered to be highly unpredictable as to what the effects of PRF1 expression inhibition would have been in vivo in tumor or precancerous cells generally. This unpredictability is borne out in the post filing art (DeYoung, Lapointe, above) which suggests that PRF1 is a tumor suppressor in breast tumor cells, and is underexpressed

in primary prostate carcinoma cells. Accordingly, one of skill in the art at the time of the invention could not have known generally in which primary tumor or precancerous cells in vivo the invention would function as claimed. Because the specification and prior art do not provide information as to how to predict which tumor or precancerous cells will be inhibited by PRF1 siRNA, one of skill in the art would have had to perform undue experimentation in order to practice the invention as claimed.

Delivery of siRNA In Vivo

Even if Applicant overcome the rejection set forth above, the enabled scope of the claimed invention will be limited to methods in which the siRNA is administered directly to the site of the tumor or precancerous growth for the reasons of record, reiterated below.

Those of skill in the art at the time of the invention, and after the invention, recognized significant obstacles related to the predictability of inhibiting expression of a target gene *in vivo* by RNA interference (RNAi), particularly in regards to the *in vivo* targeting and delivery of specific nucleic acids that mediate RNAi to the appropriate cell/organ, at a bio-effective concentration and for a period of time such that said molecule is effective in inhibiting expression of a target gene. Indeed, nucleic acid based therapies at the time of filing were highly unpredictable and while it is recognized that introduction of dsRNA targeted to a specific gene may result in expression inhibition, the successful delivery of dsRNA to a target cell *in vivo*, such that the

requisite biological effect was provided to the target cells/tissues/organs, must be determined empirically.

The state of the art at the time of filing shows that RNA interference was recognized as not enabled for therapeutic purposes. (See for example, Caplen 2003, Expert Opin. Biol. Ther. 2003, Vol. 3, pp. 575-586; Coburn et al. 2003, Journal of Antimicrobial Chemotherapy. Vol. 51, pp. 753-756; Agami et al. 2002 Current Opinion in Chemical Biology. Vol. 6, pp. 829-834) for reviews on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes).

Opalinska et al. (Nature Reviews Drug Discovery, 2002, Vol. 1, pp. 503-514) stated, "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA", and in column 2 of the same page, "[a]nother problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Caplen (2003) taught out that, "[m]any of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system…". (pg. 581).

Coburn et al. (2003) taught that the major impediment to using RNA interference as a therapeutic is that suppression of gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph).

Check (Nature, 2003, Vol., 425, pp. 10-12) reported "…scientists must figure out how to make RNAi therapies work. They are facing some formidable technical barriers, chief among which is the problem of getting siRNAs into the right cells. This is not a trivial issue, because RNA is rapidly broken down in the bloodstream and our cells don't readily absorb it through their membranes. And even when RNA gets into its target cell, scavenger proteins quickly chew it up." (see page 11, middle column, second full paragraph). Check describes that delivery methods are of concern to many researchers. In column 2 of page 11: " …'The major hurdle right now is delivery, delivery, delivery' says Sharp" and in column 3 of the same page, "Khvorova believes that the medical benefits of RNAi will be huge if the delivery issues can be resolved. 'But we've looked at a lot of the delivery methods that have been used for antisense, and so far I haven't been impressed,' she says."

After the time of the invention, Zhang et al (Current Pharmaceutical Biotechnology 2004, Vol. 5, pp.1-7) reviewed the state of the art with regard to RNAi, and stated "[u]se of siRNA in mammalian cells could be just as far-reaching, with the applications extending to functional genomics and therapeutics. But various technical issues must be addressed, especially for large-scale applications. For instance, dsRNA can be delivered to *C. elegans* by feeding or soaking, but effective delivery of siRNAs to mammalian cells will not be so simple."

Thus it is abundantly clear that it was not routine prior to and after the time of the invention for those of skill in the art to perform therapy by delivery of siRNA to target cells in vivo, particularly by methods other than those that allow delivery directly to the target cells.

In particular regards to Applicant's *ex vivo* example, often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism). For example, Agrawal et al (Agrawal et al. (Mol. Med. Today 6:72-81, 2000) stated "[t]he cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....*in vitro*, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discussed these factors in relation to antisense, but they would also apply to dsRNA. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would

not predictably translate to *in vivo* results (see p 79-80, section entitled "Cellular uptake facilitators for *in vitro* studies").

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed does not disclose any delivery formulations or techniques that were not available in the prior art, and so does not adequately address the state of the art at the time of the invention with regard to siRNA delivery to target cells in vivo.

Given the recognized unpredictability in the art of nucleic acid therapeutics, one of skill would still require specific guidance to practice the claimed methods *in vivo* in any organism or any mammal, with the resultant specified biological effect. However, the specification does not provide either examples or the required guidance to allow one of skill in the art to reliably and predictably obtain success using the claimed methods *in vivo.* The specification does not overcome the art recognized obstacles to *in vivo* RNAi, particularly in terms of specific targeting and delivery of the dsRNA to a whole organism. As a result one of skill in the art would have to perform undue experimentation in order to practice the claimed invention.

Based on the instant disclosure, one of skill in the art would not know, *a priori,* if practicing of the instant method comprising introducing a siRNA of the invention, *in vivo,* to a whole organism, would result in the successful inhibition of the target gene in any particular cell, tissue or organ of said organism. Thus one of skill in the art could not practice the invention commensurate in scope with the clams.

Response to Arguments

Applicant's arguments filed 7/23/08 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 8-10 of the response, and arguments are directed to the issue of systemic vs. local delivery.

Applicant asserts that the references cited in the rejection fail to establish a lack of enablement, pointing specifically to Table 1 of Opalinska which presents the outcomes of clinical trials. This is unpersuasive because Table 1 of Opalinska shows that the vast majority of a variety of patients treated by systemic administration of a variety of nucleic acid drugs did not show disease remission. Accordingly, it was far more likely than not that the such drugs could not be used to treat disease by systemic administration. Furthermore, the cited references make clear that those of skill in the art considered delivery of oligonucleotide drugs to be a major problem standing in the way of successful therapeutic use, and that one of skill could not predictably obtain success by systemic delivery due to problems associated with targeting, uptake, and degradation.

Applicant asserts that several of the references review problems encountered in trying to move nucleic acid-based therapies from the laboratory to the clinic, and that these references are relevant to patentability. Applicant essentially argues that the office is requiring clinical effectiveness. The Office is not requiring clinical effectiveness. Instead, the Office has cited a number of review articles that all indicate that nucleic acid based therapies generally suffer from problems associated with delivery, uptake,

and degradation of the drugs. These problems are seen by those of skill the art as barriers to effective use of these drugs in vivo. Such problems are evidence of the level of unpredictability associated with the claimed invention. The evidence of record indicates that it is far more likely than not that one of skill would not achieve success in treating a tumor or precancerous growth using systemic delivery of oligonucleotide drugs. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635